1.1. Azathioprine and photosensitivity reactions – an update

Introduction

Azathioprine (Imuran®) is registered in the Netherlands since 1968 for use as *immunosuppressant both after transplantation as in autoimmune or chronic inflammatory diseases*. It is used as monotherapy but often in combination with other medication (usually corticosteroids) and methods *influencing immune response for rheumatoid arthritis, pemphigus vulgaris, chronic refractory idiopathic thrombocytopenic purpura, systemic lupus erythematodes, M. Crohn and colitis ulcerosa*. It is used usually in combination with corticosteroids and/or other interventions is indicated for *dermatomyositis, polymyositis, polyarteritis nodosa, chronic active hepatitis and haemolytic anaemia (auto-immune basis*). It is also used to *enhance the survival of organ transplants.*

Azathioprine is an immunosuppressive antimetabolite pro-drug. It is converted into 6-mercaptopurine in the body where it blocks purine metabolism and DNA synthesis.

Azathioprine and long-wave ultraviolet light have been shown to have a synergistic clastogenic effect in patients treated with azathioprine for a range of disorders. As is usual for patients with an increased risk of skin cancer, exposure to sunlight and UV light should be limited and patients should wear protective clothing and use sunscreen with a high protection factor. Photosensitivity reactions are not mentioned in the SmPC of azathioprine [1].

Lareb informed the Medicines Evaluation Board (MEB) in Quarterly Report 2008-1 about the association between azathioprine and photosensitivity reactions [2]. Since then, seven similar reactions have been reported which are described in this update of the previous signal. Also new literature on the mechanism of this reaction has become available.

Reports

Between 30-05-1994 and 30-07-2014, the database of the Netherlands Pharmacovigilance Centre Lareb contained 17 reports of photosensitivity reaction following use of azathioprine.

patient number, sex, age, reporter	**dose indication for use**	**concomitant medication**	**ADR**	**time to onset, action taken with drug, outcome**	**remarks**
A 9228 F, 61-70 specialist doctor	azathioprine 50 mg 2DD rheumatoid arthritis	naproxen	photosensitivity reaction	3 weeks withdrawn not specified	reported as itch, dermatitis and oedema after exposition to the sun during a stay in Spain
B 32340 F, 41-50 general practitioner	azathioprine 100 mg 1DD ulcerative colitis	omeprazole, misoprostol, oxazepam, triamcinolon cream	photosensitivity reaction, skin infection	unknown, unknown unknown	

patient number, sex, age, reporter	dose indication for use	concomitant medication	ADR	time to onset, action taken with drug, outcome	remarks
C 40107 F,21-30 pharmacist	azathioprine 150mg 1DD Crohn's disease	desogestrel, diclofenac, calcium carbonate, colecalciferol	photosensitivity reaction	unknown, dose not changed, recovered	reaction was treated with fexofenadine
D 49699 F,21-30 pharmacist	azathioprine 1x 75/1x 25 mg Crohn's disease	calciumcarbo-nate, colecalciferol, ferro gradumet	photosensitivity reaction	unknown, dose not changed, recovered	two episodes of dermatitis related to the use of a sun bed
E 50596 F, 21-30 specialist doctor	azathioprine 100mg 1 DD ulcerative colitis	-	photosensitivity reaction	4 months, dose not changed, not recovered	symptoms were treated with a sun block
F 58891 F, 21-30 consumer	azathioprine 150 mg 1 DD Crohn's disease	esomeprazole, metoprolol, ferrofumarate, psyllium	photosensitivity reaction	7 months, withdrawn, recovering	
G 61333 M, 31-40 consumer	azathioprine 75mg 1DD ulcerative colitis	-	photosensitivity reaction	1 year, temporarily withdrawn, recovered	symptoms treated with cetirizine, prior episode of dermal reaction. reaction occurred after using a sunbed.
H F,61-70 65720 consumer	azathioprine 150mg 1DD Crohn's disease	mesalazine, calcium carbonate, hydrocobalamin	photosensitivity reaction alopecia	3 weeks, withdrawn, unknown	urticarial rash on hands, arms and neck
I 65899 F, 31-40 pharmacist	azathioprine 50 mg 3DD rheumatoid arthritis	enalapril, ethinylestradiol/ levonorgestrel	photosensitivity reaction	16 months	use of a sun bed and exposition to sun light
J 60528	azathioprine 50 mg 1DD		photosensitivity	1 year,	treated with sun block

patient number, sex, age, reporter	dose indication for use	concomitant medication	ADR	time to onset, action taken with drug, outcome	remarks
F, 21-30 consumer	Crohn's disease		allergic reaction, naevus	dose reduced, not recovered	
K 90877 M, 41-50, consumer	azathioprine 50mg mesalazine 1g, 4 DF colitis ulcerative		scleritis, photosensitivity reaction	5 years, dose not changed, not recovered	in winter the reaction is less or does not occur. Treated with hydro-cortisone ointment. Also photosensitivity during previous use
L 131939 F, 21-30, specialist doctor	azathioprine, 125 mg 1 DF Crohn's disease		photosensitivity reaction, urticaria	1 year, withdrawn, recovering	
M 119115 F, 41-50, pharmacist	azathioprine 200 mg 1DF Crohn's disease	mesalazine, telmisartan,, ethinylestradiol/levonorgestrel	pruritus, photosensitivity reaction	7 months, dose not changed, recovered	reaction occurred while using a solar bed, treated with antihistaminic drugs
N 179305 F, 11-20, consumer	azathioprine 100 mg 1 DF Crohn's disease		photosensitivity reaction	4 months, dose not changed, not recovered	
O 179366 F, 31-40, consumer	mesalazine 1g 2DF, azathioprine 25 mg 1 DF Crohn's disease	cyanocobalamine	photosensitivity reaction, cervical dysplasia	1 year, dose not changed, not recovered	
P 179296 F, 21-30, consumer	azathioprine 150 mg 1 DF colitis ulcerative	mesalazine	photosensitivity reaction	3 years, dose not changed, not recovered	
Q 179381 F, 31-40, consumer	azathioprine 150 mg 1 DF Crohn's disease		photosensitivity reaction	4 years, dose not changed, not recovered	reaction first occurred after 4 years but became increasingly worse the next two years, reaction confirmed by dermatologist

Other sources of information

SmPC

Photosensitivity reactions are not described in the SmPC for azathioprine. Yet its mutagenic effects when the patient is exposed to sunlight are mentioned. In this perspective it is advised in section 4.4 of the SmPC to avoid sunlight when using azathioprine [1].

Literature

Perret *et al.* [3] investigated their previous finding that azathioprine metabolites interact with ultraviolet (UV) A radiation to form promutagenic oxidative DNA damage and to determine whether this may be causal or contributory to the development of excess skin cancers post-transplantation. Five patients were recruited and the minimal erythema dose (MED) for UVB, UVA and solar-simulated radiation (SSR) was determined for each person before, and at least 12 weeks after, starting azathioprine therapy. In all five patients azathioprine treatment was associated with an increased UVA and SSR sensitivity of the skin and a significant reduction in MEDs for UVA and SSR. No change was found in UVB-induced erythema or MED. In addition, the study found that DNA from the skin of patients on azathioprine contains 6-thioguanine (6-TG).

Hofbauer *et al*. [4] measured skin photosensitivity to UVA and UVB in 48 kidney transplant patients immunosuppressed either by azathioprine (n = 32) or mycophenolate (n = 16). In 23 patients, azathioprine was subsequently replaced by mycophenolate and skin photosensitivity, DNA 6-TG content in peripheral blood mononuclear cells, and susceptibility to UVA-induced DNA damage were monitored for up to 2 years. The mean minimal erythema dose to UVA on azathioprine was twofold lower than on mycophenolate. Three months after replacing azathioprine by mycophenolate mofetil, the minimal erythema dose to UVA had increased from 15 to 25 J/cm(2) ($p < 0.001$) accompanied by reduced DNA 6-TG content. P53 protein expression in irradiated skin indicated reduced susceptibility to UVA-induced DNA damage. 6-TG DNA in peripheral blood mononuclear cells remained measurable for over 2 years. Replacing azathioprine selectively reduced the skin photosensitivity to UVA, attenuated UVA-induced skin DNA damage, and is likely based on incorporated 6-TG in DNA.

Databases

Table 2. Reports of photosensitivity associated with the use of azathioprine in the Lareb, WHO and Eudravigilance database [5-7].

Database	Number of reports	ROR (95% CI)
Lareb	17	10.7 [6.5-17.4]
WHO	80	1.8 [1.3-2.8]
Eudravigilance	28	2.1 [1.4 – 3.0]

Prescription data

Table 3. Number of patients using azathioprine in the Netherlands between 2009 and 2013 [8].

Drug	2009	2010	2011	2012	2013
azathioprine	23,803	24,989	26,042	26,959	27,378

Mechanism

Attard *et al*. [9] describe that the thiopurines azathioprine, 6-mercaptopurine and 6-thioguanine (6-TG) are important medications for cancer and inflammatory disorders and immunosuppressants in organ transplant patients. Their metabolism results in the incorporation of 6-TG into patients' DNA, and this increases skin sensitivity to incident UVA. Unlike the canonical DNA bases, which do not absorb UVA to a significant degree, DNA 6-TG is a strong UVA chromophore. It acts as a Type II UVA photosensitizer, and the combination of 6-TG and UVA treatment induces a synergistic toxicity in cultured human cells. Photochemical activation of DNA 6-TG triggers DNA and protein oxidation; it induces DNA breakage, DNA crosslinking, oxidation of DNA bases and the covalent attachment of proteins to DNA. Many of these photochemical DNA lesions are difficult for cells to deal with.

The findings of Perret *et al*. [3] confirm the presence of DNA 6-TG in the skin of those taking therapeutic doses of azathioprine and provide support for the hypothesis that DNA damage occurs when DNA 6-TG interacts with UVA, resulting in abnormal cutaneous photosensitivity.

Discussion and conclusion

In this update of a previous signal on the association between azathioprine and photosensitivity, 17 cases are described. Lareb has also reported on the association between mercaptopurine, which is azathioprine's active metabolite, and photosensitivity [10]. The fact that azathioprine's active metabolite can also cause photosensitivity further strengthens this association. The association between azathioprine and photosensitivity is supported by a significant reporting odds ratio (ROR) in the Lareb, WHO- and Eudravigilance databases and furthermore by a known mechanism and descriptions in the literature. The reporting odds ratio in the Lareb database is higher than those in the WHO- and Eudravigilance database. Many countries have only sent serious ADRs to Eudravigilance and most likely photosensitivity will be reported as a non-serious ADR.

In several of the above mentioned cases exposition to UVA in a sun bed was a contributing factor in occurrence of dermal symptoms. Apparently the advice to avoid UVA exposure is difficult to follow for patients. Reported latencies in some of the cases are longer than one year, changes in sun exposition or other unknown factors could play a role.

The previous Quarterly Report [2] described inflammatory bowel disease activity as a potential confounder since this can lead to reduction in intestinal niacin absorption. Symptoms resemble dermal lesions in pellagra, a disorder characterized by a deficiency in niacin (vitamin B3), due to dietary unbalances, or to malabsorption or to ingestion of substances blocking Niacin metabolism [11]. 6-MP is implicated in blocking this pathway, and thus increases the chance for dermal lesions during sunlight exposure in inflammatory bowel disease [12]. Yet two of seventeen patients with photosensitivity used azathioprine for rheumatoid arthritis and in the remaining patients no signs of increased disease activity, like extensive diarrhoea or intestinal surgery were mentioned.

In 7 out of the 17 cases concomitant medication was used like mesalazine, naproxen and enalapril, for which photosensitivity is also described in the literature [12-17]. A role of these drugs in causing the reaction cannot be ruled out.

Hofbauer *et al*. [4] describe that hazards associated with AZA treatment persist for many months after switching to an alternative immunosuppressant. If the skin retains similar DNA 6-TG levels, it would maintain some UVA photosensitivity and would be at risk for chronic low-level DNA photodamage. Persistent or chronic DNA damage is linked to the development of cancer.

In conclusion, the relation between azathioprine and photosensitivity is supported by case-reports, disproportionality in databases and literature and should therefore be mentioned in the SmPC.

- Photosensitivity should be mentioned in the SmPC of azathioprine

References

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This signal has been raised on July 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl